

WHAT IS CLAIMED IS:

1. A lipid compound and salts, solvates and hydrates thereof, comprising a hydrophobic tail portion covalently linked to a hydrophilic head portion, wherein said hydrophilic head portion comprises:

a first region proximal to said hydrophobic tail portion having a net positive charge at physiological pH;

a second region distal to said hydrophobic tail portion having a net negative charge at physiological pH; and

a disulfide bond connecting said first and second charged regions.

2. A lipid compound according to claim 1, wherein said tail portion comprises a saturated or unsaturated aliphatic hydrocarbon chain of 3 to 30 carbon atoms in length.

3. A lipid compound according to claim 1, wherein said hydrophobic tail portion comprises a pair of aliphatic hydrocarbon chains, each chain independently saturated or unsaturated having a length of 3 to 30 carbon atoms.

4. A lipid compound according to claim 3, wherein said aliphatic hydrocarbon chain is selected from oleyl, linoleyl, linolenyl, stearyl, eleostearyl, lauryl and palmityl.

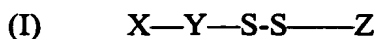
5. A lipid compound according to claim 1, wherein said tail portion comprises a steroid moiety.

6. A lipid compound according to claim 5, wherein said steroid molecule is cholesterol.

7. A lipid compound according to claim 1, wherein said head portion is peptidic.

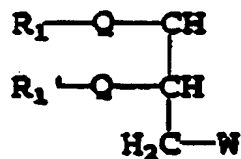
8. A lipid compound according to claim 1, wherein said head portion comprises a targeting moiety.

9. A lipid compound and salts and hydrates thereof having the formula (I):



wherein:

X is selected from



and  $R_2-Q$

$R_1$  and  $R_1'$  are independently selected from straight or branched  $C_{3-30}$  alkyl, alkenyl and alkynyl;

Q is O, OC(O), C(O)O, HNC(O), C(O)NH, OC(O)NH, or C(O);

W is  $CHR_3$ ,  $NR_3$ ,  $-N^+(R_3)_2$ , O, S,  $-C(O)NH-$ ,  $-NH(CO)-$ ,  $-OC(O)NH-$  or  $-O-P(O)(OR_3)-O-$ ;

$R_2$  is the same as  $R_1$  or is a steroid group;

$R_3$  is H or  $C_{1-4}$  alkyl;

Y is  $C_{1-12}$  alkylene,  $C_{2-12}$  alkenylene or  $C_{2-12}$  alkynylene each optionally substituted with alkyl, amino, aminoalkyl, guanidino, guanidinoalkyl, amidino or amidinoalkyl, and optionally interrupted with  $-NR_3-$ ,  $-N^+(R_3)_2-$ ,  $-C(O)-$ ,  $-NH-C(NH)-$ ,  $-C(NH)NH-$  or  $-NH-C(NH)-NH-$ , or Y is an amino acid residue or a peptide; and

Z is a  $C_{1-12}$  alkyl,  $C_{2-12}$  alkenyl,  $C_{2-12}$  alkynyl each optionally substituted with alkyl, carboxyl, carboxyalkyl, an amino acid residue, a peptide, or a targeting molecule attached via a linking group;

provided that at physiological pH, X and Y together have a net positive charge and Z has a net negative charge.

10. A lipid compound according to claim 9, wherein  $R_1$  is selected from lauryl, myristyl, palmityl, stearyl, oleyl, elaidyl, linoleyl, linolenyl, eleostearyl and phytanyl, and  $R_2$  is cholesterol.

11. A lipid compound according to claim 9, wherein  $R_1$  is oleyl or stearyl.

12. A lipid compound according to claim 9, wherein W is  $-N^+(R_3)_2-$  and  $R_3$  is  $C_{1-4}$  alkyl.

13. A lipid compound according to claim 12, wherein Y is  $C_{1-12}$ -ia alkylene,  $C_{2-12}$  alkenylene or  $C_{2-12}$  alkynylene optionally is substituted with alkyl, amino, aminoalkyl, guanidino, guanidinoalkyl, amidino or amidinoalkyl, and optionally interrupted with  $-NR_3-$ ,  $-N^+(R_3)_2-$ ,  $-C(O)-$ ,  $-NH-C(NH)-$ ,  $-C(NH)NH-$  or  $-NH-C(NH)-NH-$ .

14. A lipid compound according to claim 13, wherein Y is  $C_{1-12}$  alkylene.

15. A lipid compound according to claim 9, wherein W is  $-O-P(O)(OR_3)-O-$  and  $R_3$  is H or  $C_{1-4}$  alkyl.

16. A lipid compound according to claim 15, wherein  $R_3$  is  $C_{1-4}$  alkyl.

17. A lipid compound according to claim 15, wherein  $R_3$  is  $C_{1-4}$  alkyl.

18. A lipid compound according to claim 15, wherein Y is  $C_{1-12}$ alkylene,  $C_{2-12}$  alkenylene or  $C_{2-12}$  alkynylene optionally substituted with alkyl, amino, aminoalkyl, guanidino, guanidinoalkyl, amidino or amidinoalkyl, and optionally interrupted with  $-NR_3-$ ,  $-N^+(R_3)_2-$ ,  $-C(O)-$ ,  $-NH-C(NH)-$ ,  $-C(NH)NH-$  or  $-NH-C(NH)-NH-$ .

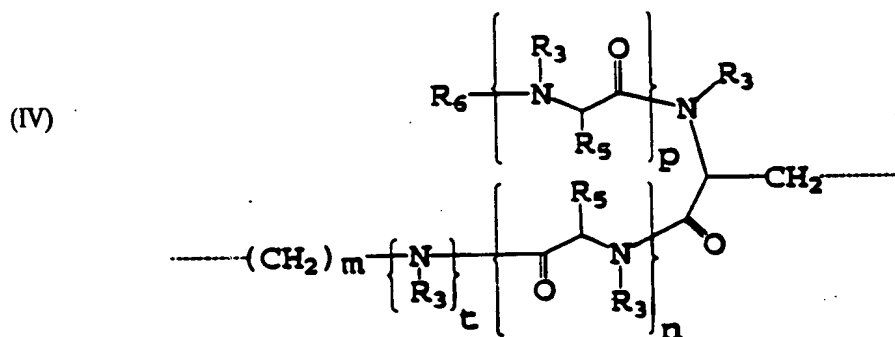
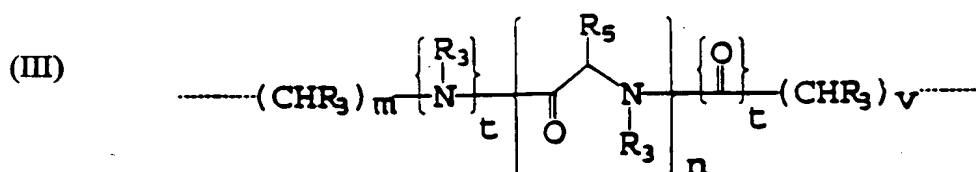
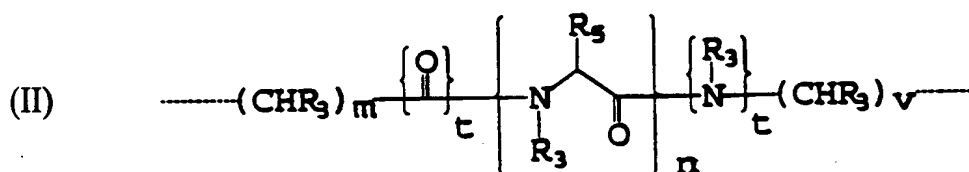
19. A lipid compound according to claim 18, wherein Y is  $C_{1-6}$  alkylene interrupted with  $-N^+(R_3)_2-$  wherein  $R_3$  is  $C_{1-4}$ .

20. A lipid compound according to claim 9, wherein W is O and Y is C<sub>1-12</sub> alkylene, C<sub>2-12</sub> alkenylene or C<sub>2-12</sub> alkynylene optionally substituted with alkyl, amino, aminoalkyl, guanidino, guanidinoalkyl, amidino or amidinoalkyl, and optionally interrupted with -NR<sub>3</sub>-, -N<sup>+</sup>(R<sub>3</sub>)<sub>2</sub>-, -C(O)-, -NH-C(NH)-, -C(NH)NH- or -NH-C(NH)-NH-.

21. A lipid compound according to claim 20, wherein Y is C<sub>1-6</sub> alkylene interrupted with -C(O)-, -NH- and -NH-C(NH)-.

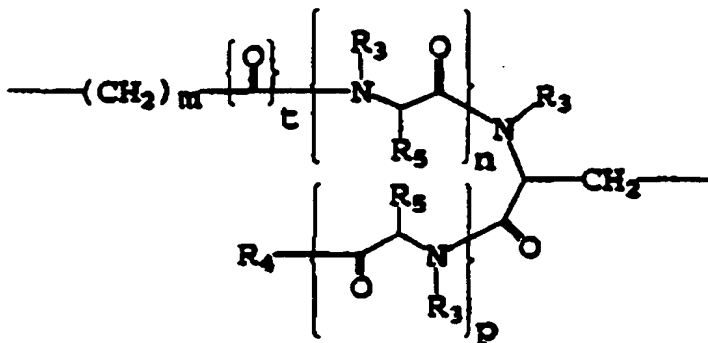
22. A lipid compound according to claim 21, wherein Y is -C(O)-NH-(CH<sub>2</sub>)<sub>2</sub>-NH-C(NH)-(CH<sub>2</sub>)<sub>3</sub>-.

23. A lipid compound according to claim 9, wherein Y is an amino acid residue or a peptide group selected from:



and

(V)



wherein

$R_4$  is H, OH,  $N(R_3)_2$ , or  $C_{1-4}$  alkyl;

$R_5$  is independently an amino acid side chain;

$R_6$  is H,  $C_{1-4}$  alkyl or  $C_{1-4}$  acyl;

$m$  is an integer from 0 to 30;

$n$  is an integer from 1 to 100;

$o$  is an integer from 1 to 30;

$p$  is an integer from 0 to 100; and

$t$  is an integer 0 or 1.

24. A lipid compound according to claim 23, wherein  $t$  is 1.

25. A lipid compound according to claim 23, wherein  $m$  and  $v$  are independently an integer from 1 to 4.

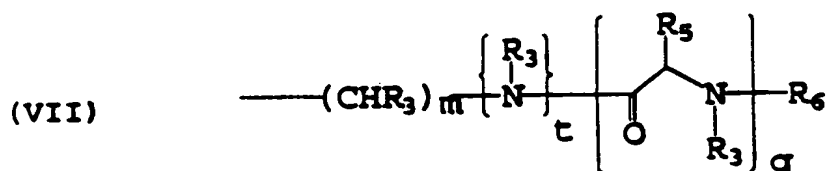
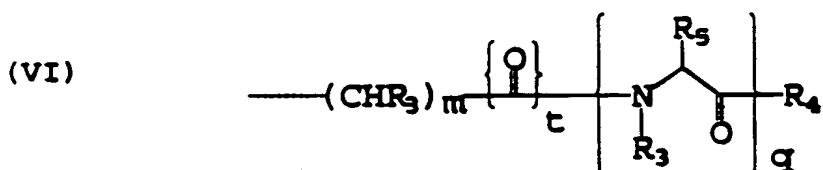
26. A lipid compound according to claim 23, wherein  $n$  is an integer from 1 to 15.

27. A lipid compound according to claim 23, wherein  $p$  is an integer from 0 to 15.

28. A lipid compound according to claim 23, wherein  $R_3$  is H.

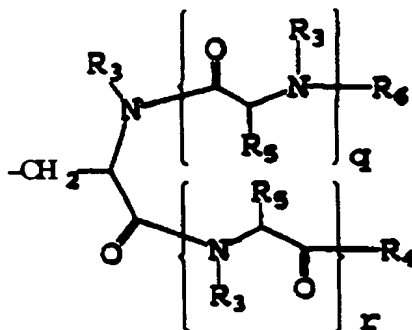
29. A lipid compound according to claim 23, wherein  $R_4$  is  $NH_2$ .

30. A lipid compound according to claim 23, wherein  $R_6$  is H.
31. A lipid compound according to claim 23, wherein at least one  $R_5$  is a side chain of amino acids lysine and arginine.
32. A lipid compound according to claim 9, wherein Z is a targeting molecule attached via a linking group.
33. A lipid compound according to claim 32, wherein said targeting molecule is a cell surface receptor ligand.
34. A lipid compound according to claim 33, wherein said targeting molecule is folate.
35. A lipid compound according to claim 34, wherein said linking group is polyethylene glycol (PEG).
36. A lipid compound according to claim 32, wherein said targeting molecule is a peptide, protein or saccharide.
37. A lipid compound according to claim 36, wherein said targeting molecule is an antibody.
38. A lipid compound according to claim 37, wherein said 10 antibody is a monoclonal antibody.
39. A lipid compound according to claim 9, wherein Z is an amino acid residue or a peptide group selected from:



and

(VIII)



wherein

R<sub>3</sub> is H or C<sub>1-4</sub> alkyl;

R<sub>4</sub> is H, OH, N(R<sub>3</sub>)<sub>2</sub>, or C<sub>1-4</sub> alkyl;

R<sub>5</sub> is independently an amino acid side chain;

R<sub>6</sub> is H, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> acyl;

m is an integer from 1 to 30;

q and r are both independently an integer from 0 to 200 and the sum of q and r is from 1 to 200; and

t is an integer 0 or 1.

40. A lipid compound according to claim 39, wherein t is 1.

41. A lipid compound according to claim 39, wherein m is an integer from 1 to 4.

42. A lipid compound according to claim 39, wherein q is an integer from 1 to 20.

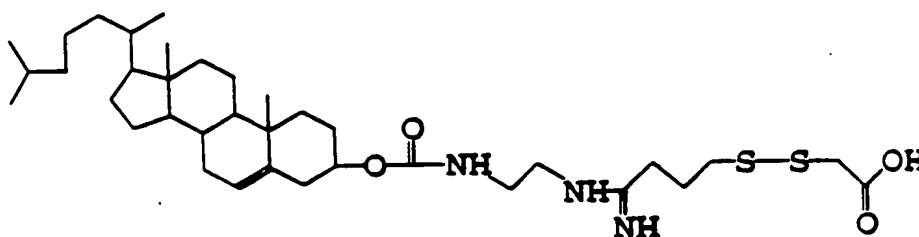
43. A lipid compound according to claim 39, wherein r is an integer from 1 to 20.

44. A lipid compound according to claim 39, wherein R<sub>4</sub> is OH.

45. A lipid compound according to claim 39, wherein  $R_6$  is methyl or acetyl.

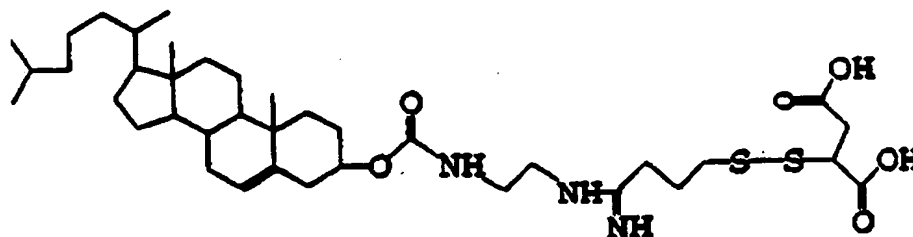
46. A lipid compound according to claim 39, wherein at least one  $R_5$  is a side chain of amino acids aspartate or glutamate.

47. A lipid compound according to claim 1, which is



and salts, solvates and hydrates thereof.

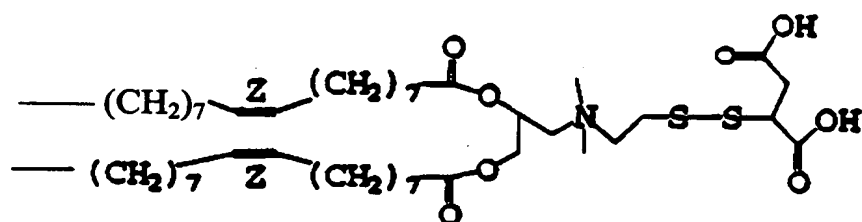
48. A lipid compound according to claim 1, which is



and salts, solvates and hydrates thereof.



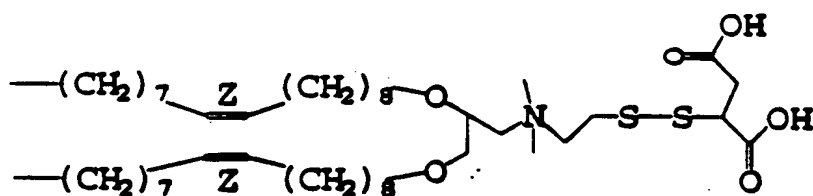
49. A lipid compound according to claim 1, which is



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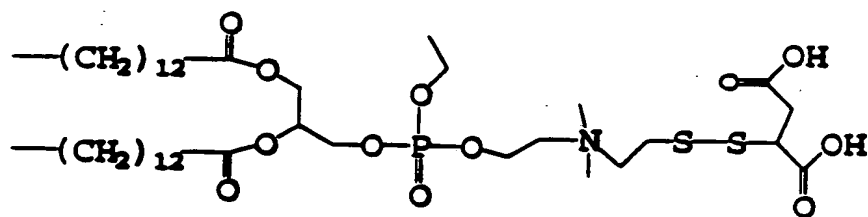
and salts, solvates and hydrates thereof.

50. A lipid compound according to claim 1, which is



and salts, solvates and hydrates thereof.

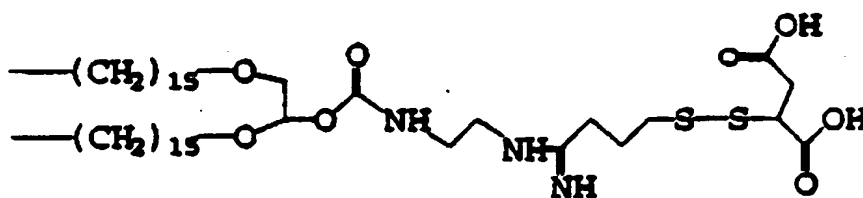
51. A lipid compound according to claim 1, which is



and salts, solvates and hydrates thereof.

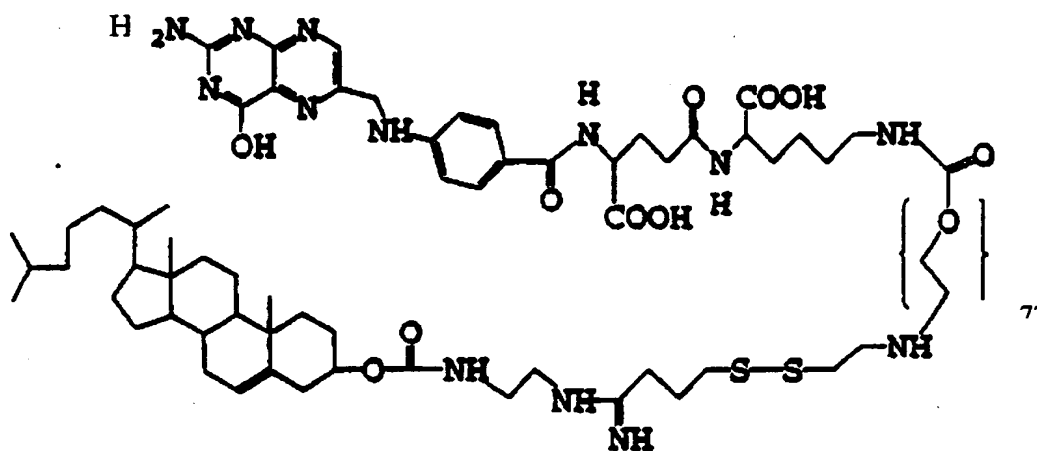
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52. A lipid compound according to claim 1, which is



and salts, solvates and hydrates thereof.

53. A lipid compound according to claim 1, which is



and salts, solvates and hydrates thereof.

54. A liposome comprising a lipid according to claim 1.

55. A liposome according to claim 54, wherein said lipid is present in an amount of about 5 to 80 mole percent.

56. A liposome according to claim 54, wherein said lipid is present in an amount of about 20 to 70 mole percent.

**ISIS-5023 PATENT**

57. A liposome according to claim 54, wherein said lipid is present in an amount of about 30 to 60 mole percent.

58. A liposome according to claim 54, wherein said lipid is present in an amount of about 40 to 55 mole percent.

59. A liposome according to claim 54, further comprising a pharmaceutical agent encapsulated within said liposome.

60. A liposome according to claim 59, wherein said pharmaceutical agent is a therapeutic, prophylactic or diagnostic compound.

61. A liposome according to claim 60, wherein said pharmaceutical agent is selected from a nucleoside, nucleotide, oligonucleotide, amino acid, peptide, polypeptide and protein or derivatives thereof.

62. A liposome according to claim 61, wherein said pharmaceutical agent is an oligonucleotide.

63. A liposome according to claim 54, further comprising a targeting molecule linked to the exterior of said liposome.

64. A liposome according to claim 63, wherein said targeting molecule is selected from proteins.

65. A liposome according to claim 63, wherein said targeting molecule is folate.

66. A liposome according to claim 65, wherein said targeting molecule is linked to a lipid by a polyethylene glycol linker.

67. A method of delivering a pharmaceutical agent to an animal, comprising administering to said animal an effective amount of a liposome according to claim 54.

68. The method according to claim 67, wherein said liposome is administered enterally.

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69. The method according to claim 68, wherein said liposome 25 is administered orally.

70. The method according to claim 67, wherein said liposome is administered by pulmonary inhalation.

71. The method according to claim 67, wherein said liposome is administered parenterally.

72. The method according to claim 71, wherein said liposome is administered by intravenous injection.

73. The method according to claim 71, wherein said liposome is administered by subcutaneous injection.

74. The method according to claim 71, wherein said liposome is administered by intramuscular injection.

75. The method according to claim 67, wherein said liposome is administered topically.

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and  
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